

1 **MRSA Surveillance Programmes Worldwide: Moving towards a harmonised international**  
2 **approach**

3  
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74 **Abstract**

75 Multinational surveillance programmes for methicillin-resistant *Staphylococcus aureus* (MRSA) are  
76 dependent on national structures for data collection. This study aimed to capture the diversity of  
77 national MRSA surveillance programmes and propose a framework for harmonisation of MRSA  
78 surveillance.

79

80 The International Society of Antimicrobial Chemotherapy (ISAC) MRSA Working Group conducted  
81 a structured survey on MRSA surveillance programmes and organised a webinar to discuss the  
82 programmes' strengths and challenges and guidelines for harmonisation.

83

84 Completed surveys represented 24 MRSA surveillance programmes in 16 countries. Several countries  
85 reported separate epidemiological and microbiological surveillance. Informing clinicians and national  
86 policymakers were the most common purposes of surveillance. Surveillance of bloodstream infections  
87 (BSI) was present in all programmes. Other invasive infections were often included. Three countries  
88 reported active surveillance of MRSA carriage. Methodology and reporting of antimicrobial  
89 susceptibility, virulence factors, molecular genotyping and epidemiological metadata varied greatly.

90

91 Current MRSA surveillance programmes rely upon heterogeneous data collection systems, which  
92 hampers international epidemiological monitoring and research. To harmonise MRSA surveillance,  
93 we suggest improving the integration of microbiological and epidemiological data, implementation of  
94 central biobanks for MRSA isolate collection, and inclusion of a representative sample of skin and  
95 soft tissue infection cases in addition to all BSI cases.

96

97 **Keywords:** Antimicrobial resistance, *Staphylococcus aureus*, monitoring, epidemiology

98

99

100 **1. Introduction**

101 Antimicrobial resistance (AMR) is one of the greatest threats to public health. Methicillin-resistant  
102 *Staphylococcus aureus* (MRSA) is the second most common cause of antibiotic-resistant bacterial  
103 infection in the European Union (EU) and European Economic Area (EEA) [1]. Many MRSA  
104 originate from a limited number of historically dominant clonal lineages [2]. While some MRSA  
105 clones are found worldwide, others are restricted to certain geographic areas, implying differences in  
106 transmission [3]. To analyse MRSA transmission and to decrease the incidence of new infections,  
107 international epidemiological research is crucial, and this research depends on MRSA surveillance  
108 programmes.

109

110 Many MRSA surveillance programmes exist worldwide, but only a few are multinational [4]. One  
111 European multinational programme is the European Antimicrobial Resistance Surveillance  
112 Network (EARS-Net) [5]. EARS-Net is coordinated by the European Centre for Disease Prevention  
113 and Control (ECDC) and depends on national surveillance systems. While susceptibility testing and  
114 interpretation recommendations have been harmonised (EUCAST) [5], national surveillance  
115 programmes use different sampling strategies and laboratory techniques that can bias analyses [6].  
116 Also, non-European multinational MRSA surveillance programmes mostly depend on national  
117 networks using different methodologies. Examples are the Asian Network for Surveillance of  
118 Resistant Pathogens (ANSORP), the Latin American Network for Antimicrobial Resistance  
119 Surveillance (ReLAVRA), the SENTRY Antimicrobial Surveillance Program and the Tigecycline  
120 Evaluation and Surveillance Trial (T.E.S.T.), now embedded in the Antimicrobial Testing Leadership  
121 and Surveillance (ATLAS) database [7-11].

122

123 Heterogeneity in testing and sampling practices hampers international epidemiological surveillance  
124 and the establishment of an early warning system for emerging MRSA clones [4,12,13]. Additionally,  
125 it lowers the quality of available data. This can be illustrated by the experiences of the MACOTRA  
126 study group, which aimed to establish an MRSA strain collection to analyse transmission success of  
127 MRSA. However, drafted definitions of successful versus unsuccessful MRSA strains were not  
128 applicable due to the heterogeneity described above. As a result, multiple strategies for strain  
129 selection were adopted, leading to selection bias and decreased data comparability. This demonstrates  
130 that the current organisation of MRSA surveillance systems and reference laboratories are not  
131 sufficient to support a greater understanding of MRSA transmission, nor to detect emerging, virulent  
132 strains.

133

134 The aim of this project was to capture the diversity of existing national and institutional MRSA  
135 surveillance programmes and propose a framework for a standardised (inter)national surveillance  
136 network. A structured survey on current MRSA surveillance practices was conducted, followed by a

137 webinar organised by the International Society of Antimicrobial Chemotherapy (ISAC) MRSA  
138 Working Group.

139

## 140 **2. Methods**

141 ISAC MRSA Working Group members were contacted to identify directors or head microbiologists  
142 of national or regional MRSA surveillance programmes or staphylococcal reference laboratories in  
143 their respective countries. Other representatives of national organisations participating in EARS-Net  
144 were contacted directly [5]. All representatives were invited to participate in a structured survey  
145 drafted by the executive committee of the ISAC MRSA Working Group (MCV (chair), MZD, HS,  
146 VB, SS). This survey contained sections about organisational structure, surveillance goals, strain and  
147 sample characteristics, epidemiological metadata and laboratory reports. An overview of the survey is  
148 given in supplementary data.

149

150 Additionally, surveillance programme representatives were invited to participate in a webinar, held on  
151 10 March 2021, organised by the ISAC MRSA Working Group and the MACOTRA study group,  
152 which was entitled: ‘Regional and National MRSA Surveillance Programs Worldwide: Results of a  
153 Survey and Discussion of Current Practices’. Its purpose was to present an overview of surveillance  
154 programmes to an international audience, discuss these programmes’ strengths and challenges, and  
155 discuss the requirements for harmonisation of MRSA surveillance.

156

## 157 **3. Results**

158 Representatives of 12 MRSA surveillance programmes in 9 countries were invited through the ISAC  
159 MRSA Working Group (Figure 1). Another 21 national organisations participating in EARS-Net were  
160 also invited. In total, 18 surveys were completed between January and April 2021, representing 24  
161 MRSA surveillance programmes in 14 European and 2 non-European countries. Multiple surveillance  
162 programmes were described for Belgium (3), Germany (3), France (2), Indonesia (2), Switzerland (2)  
163 and the United States of America (USA) (2). Fourteen surveillance programmes in 8 countries were  
164 presented at the webinar.

165

### 166 **3.1 Survey**

167 A summary of survey results is given in Table 1.

168

#### 169 **3.1.1 Surveillance structure and purpose**

170 All countries conducted surveillance at the national level, except Malta. In Malta, surveillance was  
171 performed at the sole tertiary hospital, but covered >90% of all national testing. In four countries,  
172 surveillance was primarily conducted at the hospital level and organised around the surveillance of

173 bloodstream infections (BSI). In the Czech Republic, all hospitals performed some MRSA  
174 surveillance, and MRSA BSI surveillance captured ~80% of the population. In Ireland and Poland,  
175 passive surveillance was performed through EARS-Net participation, and several national structured  
176 surveys were conducted in the past 20 years. For Indonesia, active MRSA surveillance was performed  
177 in several hospitals, but most surveillance was conducted for research purposes.

178

179 In Belgium, France and Germany, multiple separate programmes for epidemiological and  
180 microbiological surveillance were reported. In Switzerland, a local initiative focused on molecular  
181 surveillance of MRSA exists in addition to the national surveillance system, ANRESIS, which gathers  
182 epidemiological data for all antimicrobial-resistant microorganisms. In the USA, at least two large  
183 MRSA surveillance programmes exist: a national programme on MRSA BSI in which most hospitals  
184 participate and a population-based programme of invasive MRSA infections covering ~5% of the  
185 population [14].

186

187 Most surveillance programmes served multiple goals. The most common purpose of surveillance was  
188 to inform clinicians, public health workers, and laboratories about current resistance trends (17/18).  
189 Other epidemiological goals were informing national policymakers (14/18) or EARS-Net  
190 participation (for all current EU/EEA countries except Norway). Research goals included studies on  
191 staphylococcal virulence factors (12/18), resistance profiles, specific clones such as LA-MRSA, risk  
192 factor analysis, monitoring effectiveness of interventions or outbreak investigations.

193

### 194 **3.1.2 Collection of isolates, microbiological and epidemiological data**

195 Results of BSI isolates were collected in all surveillance programmes. Collection of wound (15/18),  
196 skin (12/18) or nose, throat or perineum (12/18) isolates also occurred frequently. Eleven programmes  
197 reported the inclusion of isolates from other clinical sample types, such as cerebrospinal fluid, urine,  
198 pus, sputum or all clinical samples (6/11). Active surveillance of MRSA carriage was reported only  
199 for Denmark, the Netherlands and Norway. Isolates from outpatients (9/18) and the general  
200 community (10/18) were also reported, but systematic active surveillance of these groups was  
201 performed only in Denmark, the Netherlands and Norway. Long-term storage of isolates varied,  
202 ranging from BSI isolates only to all submitted isolates. Programmes with an epidemiological focus  
203 often lacked routine isolate collection.

204

205 Most programmes collected microbiological data, such as antimicrobial susceptibilities (14/18) and  
206 the presence of virulence factors (11/18). The presence of the Pantone-Valentine leukocidin (PVL)  
207 toxin was most commonly tested (8/11). Eleven programmes performed genotyping on all isolates,  
208 with *spa* typing as the most common method (6/11). A wide range of genotyping techniques were  
209 reported: whole genome sequencing (WGS) (10/11), *spa* typing (8/11), multilocus sequence typing

210 (MLST) (6/11), pulsed-field gel electrophoresis (PFGE) (3/11), *agr* group typing (Belgium), CC398  
211 subtyping (Denmark), MLVA (Netherlands), MLVF (Poland), DNA microarray (Ireland), SCC*mec*  
212 typing (USA), CC8 subtyping (USA) and double locus sequence typing (local Swiss initiative).

213

214 Regarding epidemiological metadata, demographic variables were most commonly collected (16/18),  
215 followed by clinical information (14/18), MRSA risk factors (6/18) and outbreak metadata (4/18).

216

### 217 **3.2 Webinar**

218 The goals, strengths, challenges and future plans of ten MRSA surveillance programmes in eight  
219 countries were presented at the ISAC MRSA webinar. Strengths were the robust network of local  
220 laboratories and/or hospitals in the Czech Republic, France and Poland, as well as the national  
221 surveillance programmes in Belgium, Denmark, Germany, the Netherlands and Switzerland. In  
222 Denmark and the Netherlands, the strong collaboration between epidemiological and microbiological  
223 departments and existing WGS pipelines enhanced MRSA surveillance. However, limited  
224 collaboration between epidemiological and microbiological surveillance structures posed a major  
225 challenge for Belgium, France, Germany and Switzerland. The representatives of the Czech Republic,  
226 Denmark, Germany, the Netherlands, Poland and Switzerland advocated for the implementation of  
227 WGS as a default genotyping technique and an accompanying platform to share WGS data. For many  
228 surveillance programmes, stability of financial support was a concern.

229

230 Based on our results and webinar discussions, the ISAC MRSA Working Group, MRSA surveillance  
231 worldwide study group and the MACOTRA study group propose three suggestions to harmonise  
232 MRSA surveillance.

- 233 1. Inclusion of all BSI cases and a representative number of skin and soft-tissue infection (SSTI)  
234 cases in proportion to MRSA prevalence
- 235 2. Integration of microbiological and epidemiological data
- 236 3. Implementation of central biobanks at the national level for the collection and further  
237 characterisation of MRSA strains using common nomenclature allowing international  
238 comparisons

239

240 The challenges and our proposal for harmonised surveillance are summarised in Figure 2.

241

### 242 **4. Discussion**

243

244 Our study presents an overview of existing MRSA surveillance programmes in various parts of the  
245 world with an emphasis on European countries. It demonstrates the great diversity of MRSA

246 surveillance programmes, both in surveillance structure as well as in microbiological and  
247 epidemiological data collection. Factors potentially driving this diversity are the primary goals of  
248 surveillance, the population size, MRSA prevalence and laboratory capacity. To improve the work of  
249 these systems, a harmonised approach for surveillance programmes is needed.

250

251 We propose the inclusion of SSTI cases in addition to all BSI cases. BSI cases represent the most life-  
252 threatening MRSA infections. Because these cases are clearly defined, they provide high quality data  
253 for surveillance. Most surveillance programmes already include BSI cases.

254 MRSA BSIs are predominantly endogenous infections, preceded by carriage and/or non-invasive  
255 infections [15,16]. For this reason, it is desirable to include non-BSI cases in surveillance as well.

256 SSTIs represent the majority of *S. aureus* infections and are often acquired in the community.

257 Inclusion of SSTIs in surveillance likely increases the probability of detecting emerging clones,  
258 which may also have significant public health impact. We recommend including a representative  
259 number of SSTI cases in proportion to BSI cases and MRSA prevalence to limit selection bias. This  
260 proportion will depend on the number of estimated MRSA BSI cases within the country, considering  
261 the expected volume and thus feasibility. A clear definition of SSTI such as presented in the  
262 CDC/NHSN Patient Safety Component Manual must be used to prevent misclassification [17].

263

264 The integration of microbiological and epidemiological data should be improved to enhance data  
265 quality [4,12]. Completion of a standardised epidemiological metadata report for each submitted case  
266 is essential. In addition to demographic data (i.e., age, gender and place of residence), the sampling  
267 date and site and classification of the isolate as being from infection or colonisation are necessary.  
268 Also required is the information on relevant risk factors for MRSA acquisition to assign the  
269 patient/carrier to a defined risk group or to identify new risk factors.

270

271 The implementation of a central MRSA biobank at the national level is needed to collect isolates  
272 corresponding to the obtained epidemiological data. Typically, this biobank would be maintained by a  
273 reference laboratory, which can provide genotyping, antimicrobial susceptibility testing and testing  
274 for virulence genes on a well-defined sample of isolates. We advocate for the use of WGS as the  
275 routine genotyping technique along with common nomenclature allowing international comparisons,  
276 and incorporate detailed phylogenetic data for local, national, and international comparisons.  
277 Furthermore, we recommend repeating the structured survey undertaken by Grundmann *et al.*, to  
278 provide an update of MRSA epidemiology at the European level [18].

279

280 We advocate that professional microbiological societies support guideline development for  
281 harmonisation. Due to its focus, aims, international representation and goals, ISAC could take the lead

282 in this process. These guidelines should include BSI/SSTI definitions and a report template for  
283 epidemiological metadata. Additionally, a feasible ratio of BSI/SSTI cases for inclusion should be  
284 determined in collaboration with programme representatives. Furthermore, we recommend the  
285 development of an international repository for standardised surveillance data, including WGS data.  
286 Other suggestions for the harmonisation of AMR surveillance should be considered [4,12,19,20], such  
287 as the alignment of surveillance goals and standardised methodology for data collection, data analysis  
288 and data sharing.

289

290 Although many countries expend substantial effort and resources on MRSA surveillance, stability of  
291 financial support is a general concern. This should be recognised in guideline development as national  
292 health budgets will greatly influence the opportunities for harmonisation of surveillance programmes.

293

294 Inclusion bias may have limited the generalisability of our study results. Nevertheless, we were able  
295 to highlight the diversity of surveillance programmes, and our webinar enabled MRSA surveillance  
296 experts to discuss their differences directly. This guided the development of our proposal for the  
297 harmonisation of MRSA surveillance programmes.

298

299 In conclusion, current MRSA surveillance programmes rely upon heterogeneous data collection,  
300 which hampers international epidemiological monitoring and research. For harmonisation of MRSA  
301 surveillance, we suggest including SSTI cases in proportion to collected BSI cases, improving the  
302 integration of microbiological and epidemiological data, implementing central biobanks for the  
303 collection and further characterisation of MRSA isolates, and genotyping of a structured sample of  
304 these isolates, preferably using WGS.

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322

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- 396

397 **Figure captions**

398 **Figure 1. Overview of participating surveillance programmes**

399 Representatives of MRSA surveillance programmes were identified through the network of the ISAC  
400 MRSA working group (ISAC MRSA-WG) or through the participation in the European Antimicrobial  
401 Resistance Surveillance Network (EARS-Net). Listed are the numbers of contacted organisations and  
402 respective number of countries. Also listed are the number of returned surveys and presentations  
403 given at the webinar, for the respective number of included countries and surveillance programmes.

404 **Figure 2. Proposal for harmonised MRSA surveillance**

405 To harmonise surveillance, we propose (1) inclusion of all bloodstream infection (BSI) isolates and a  
406 representative sample of skin and soft-tissue infection (SSTI) isolates in proportion to MRSA  
407 prevalence, (2) integration of microbiological and epidemiological data in a single database using  
408 standardised report templates, and (3) implementation of central biobanks for collection and further  
409 characterisation of MRSA isolates. Orange flags depict the main challenges in harmonised  
410 surveillance.

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